EVALUATION OF TREATMENT OUTCOME, HEALTH-RELATED QUALITY OF LIFE AND COST OF TREATMENT IN SMEAR POSITIVE PULMONARY TUBERCULOSIS PATIENTS

by

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DEDICATION

This thesis is lovingly dedicated to my parents,

Muhammad Ramzan Yazdani and Surriya Yazdani,

my brother, Muhammad Asif,

my darling wife, Irem Mushtaq,

and my loving son Muhammad Danial Atif (Nana).

Their moral support, faith, love, and joy

have energized me to pursue and

accomplish my goals.

Muhammad Atif
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LIST OF ABBREVIATIONS

ABC:	Activity-Based Costing
ADA:	Adenosine Deaminase
AFB:	Acid-Fast Bacilli
AIDS:	Acquired Immunodeficiency Syndrome
ANOVA:	Analysis of Variance
BAL:	Bronchoalveolar Lavage
BCG:	Bacille Calmette–Guérin
BP:	Bodily Pain
CI:	Confidence Interval
COI:	Cost-of-Illness
CP:	Continuation Phase
CT:	Computerized Tomography
DM:	Diabetes Mellitus
DOT:	Directly Observed Therapy
DST:	Drug Sensitivity Testing
E:	Ethambutol
EPTB:	Extrapulmonary Tuberculosis
FDCs:	Fixed-Dose Combinations
GH:	General Health
GHQ-12:	General Health Questionnaire 12
H:	Isoniazid
HIV:	Human Immunodeficiency Virus
HPP:	Hospital Pulau Pinang
HRQoL:	Health-Related Quality of Life
IP:	Intensive Phase
IPT:	Isoniazid Preventive Therapy

LIST OF ABBREVIATIONS

IRGAs:	Interferon-Gamma Release Assays
ISTC:	International Standards for Tuberculosis Care
IQOLA:	International Quality of Life Assessment
IUATLD:	International Union Against Tuberculosis and Lung Disease
LOA:	Loss of Appetite
LOW:	Loss of Weight
LTBI:	Latent Tuberculosis Infection
M. tb:	Mycobacterium tuberculosis
MCID:	Minimal Clinically Important Difference
MCS:	Mental Component Summary
MDR-TB:	Multidrug-Resistant Tuberculosis
MERC	Medical Research Ethics Committee
MDGs:	Millennium Development Goals
MH:	Mental Health
MLT:	Medical Laboratory Technologist
MOH:	Ministry of Health
MRI:	Magnetic Resonance Imaging
MYR:	Malaysian Ringgit
NAATs:	Nucleic Acid Amplification Tests
NBS:	Norm-Based Scoring
NDI:	National Death Index
NGOs:	Non-Governmental Organizations
NICE:	National Institute for Health and Clinical Excellence
NIH:	National Institute of Health
NMRR:	National Medical Research Register
NTP:	National Tuberculosis Program
OTC:	Over-the-Counter
PASW:	Predictive Analytics Software

LIST OF ABBREVIATIONS

PCR:	Polymerase Chain Reaction
PCS:	Physical Component Summary
PF:	Physical Functioning
PTB:	Pulmonary Tuberculosis
R:	Rifampicin
RE:	Role-Emotion
RP:	Role-Physical
SD:	Standard Deviation
SF:	Social Functioning
SF-36v2:	Short-Form 36 Version 2
T&CM:	Traditional & Complementary Medicine
T&CMD:	Traditional & Complementary Medicine Division
TB:	Tuberculosis
TBIS:	Tuberculosis Information System
TBNET:	Tuberculosis Network European Trials Group
THB:	Thai Baht
TIMS:	Tuberculosis Information Management System
TST:	Tuberculosis Skin Test
U.S.:	United States
UK:	United Kingdom
US:	Ultrasonography
USD:	United States Dollars
VBG:	Venous Blood Gases
VT:	Vitality
WHO:	World Health Organization
XDR-TB:	Extensively Drug-Resistant Tuberculosis
Z:	Pyrazinamide

LIST OF PUBLICATIONS AND COMMUNICATIONS

Journal Publications (full length)

1. **Atif, M.,** Sulaiman, S. A. S., Shafie, A. A., Asif, M., Zaheer, B., … Low, H. C. (2014). Impact of tuberculosis treatment on health-related quality of life of tuberculosis patients: a follow-up study. *Health and Quality of Life Outcomes*, (accepted for publication).

2. **Atif, M.,** Sulaiman, S. A. S., Shafie, A. A., Asif, M., & Jamshed, S. Q. (2013). Engaging community pharmacists and alternative practitioners: a way forward to active case finding of tuberculosis in Malaysia. *Tropical Journal of Pharmaceutical Research, 12*(6), 1093-1095. doi:10.4314/tjpr.v12i6.34

3. **Atif, M.,** Sulaiman, S. A. S., Shafie, A. A., Asif, M., & Ahmad, N. (2013). SF-36v2 norms and its discriminative properties among healthy households of tuberculosis patients in Malaysia. *Quality of Life Research, 22*(8), 1955-1964. doi:10.1007/s11136-012-0337-x

4. Shafie, A. A., **Atif, M.,** Sulaiman, S. A. S, Asif, M., & Zahari, C. D. (2012). Normative data, discriminative properties and equivalence of SF-36v2 health survey in Malaysian population. *Latin American Journal of Pharmacy, 31*(8), 1117-1125. Retrieved from http://www.latamjpharm.org/previous_issue.php?vol=31&num=8

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Journal Publications (abstracts)

11. **Atif, M.,** Sulaiman, S. A. S., Shafie, A. A., Ali, I., & Ahmad, N. (2012). Tuberculin skin testing and chest X-ray for tracing tuberculosis contacts: costs and practicality. *The International Journal of Tuberculosis and Lung Disease, 16*(12)S1, S407. "Poster presented at the Union conference, November, Kuala Lumpur, Malaysia".

12. **Atif, M.,** Sulaiman, S. A., Shafie, A. A., Hassali, M. A., & Ahmad, N. (2012). SF-36v2 norms and its discriminative properties among healthy households of tuberculosis patients. *The International Journal of Tuberculosis and Lung Disease*, *16*(12)S1, S437. "Poster presented at the Union conference, November, Kuala Lumpur, Malaysia".

13. **Atif, M.,** Sulaiman, S. A. S., Hassali, M. A., Shafie, A. A., & Saleem, F. (2012). Determination of chest x-ray cost using activity based costing approach at Penang General Hospital, Malaysia. *Value in Health, 15*(4), A66. "Poster resented at the ISPOR 17th Annual International Meeting, June, Washington DCA, United States of America".

14. **Atif, M.,** Sulaiman, S. A. S., Hassali, M. A., Shafie, A. A., & Saleem, F. (2012). Health-related quality of life trajectories among general population in the state of Penang, Malaysia. *Value in Health, 15*(4), A203. "Poster resented at the ISPOR 17th Annual International Meeting, June, Washington DCA, United States of America".

Publications (abstracts in conference proceedings)

15. **Atif, M.,** Sulaiman, S. A. S., Ali, I., Muttalif, A. R., & Shafie, A. A. (2011). Drug induced vomiting and diabetes mellitus complicating management of pulmonary tuberculosis: a case report from Malaysia. "Poster presented at the Annual Congress of Malaysian Thoracic Society, Kuala Lumpur, Malaysia".

16. **Atif, M.,** Sulaiman, S. A. S., Ali, I., Muttalif, A. R., & Shafie, A. A. (2011). Are tuberculosis treatment outcome categories missing something: a case report from Malaysia. "Poster presented at the Annual Congress of Malaysian Thoracic Society, Kuala Lumpur, Malaysia".

PENILAIAN DAPATAN RAWATAN, KUALITI KEHIDUPAN YANG BERKAITAN DENGAN KESIHATAN DAN KOS RAWATAN DALAM KALANGAN PESAKIT PULMONARI TUBERKULOSIS YANG MEMPUNYAI *SMEAR* POSITIF

ABSTRAK

Walaupun terapi yang berkesan, namun tuberkulosis (TB) kekal sebagai satu daripada punca utama morbiditi dan kematian orang dewasa, terutama di negara membangun. Data yang ada menunjukkan bahawa beban TB semakin meningkat di Malaysia. Objektif kajian ini adalah untuk menilai pengurusan pesakit PTB positif smear baru. Ia termasuk pengurusan klinikal, kesihatan berkaitan kualiti kehidupan (HRQoL), dan petunjuk ekonomi di klinik dada di Hospital Pulau Pinang (HPP), Malaysia.

Dalam bahagian pertama kajian susulan prospektif ini, semua pesakit PTB positif smear baru yang berdaftar di klinik dada HPP, di antara Mac 2010 dan Februari 2011, telah dinilaikan hasil rawatan mereka. Dalam bahagian kedua, pesakit PTB daripada kohort yang sama diminta melengkapkan soal selidik (SF-36v2) HRQoL pada mana-mana masa daripada tiga masa pilihan yang diberi sepanjang rawatan mereka. Selain itu, penjaga keluarga mereka diminta melengkapkan soal selidik SF-36v2 semasa prosedur mengesan-kontak. Dalam bahagian ketiga, kajian ekonomi berasaskan insidens telah dijalankan. Jumlah kos rawatan TB dianggarkan berdasarkan perspektif pembekal dan pesakit.

Kadar kejayaan rawatan TB dalam kajian ini adalah 67.26 %, dan 17.56 % daripadanya mati semasa rawatan. Sehubungan dengan skor HRQoL dalam kalangan pesakit PTB positif smear baru, hasil kajian menunjukkan bahawa perbezaan dalam kalangan skor skala SF-36v2 pada permulaan dan akhir rawatan adalah perbezaan

minimum klinikal yang penting. Pengulangan analisis ANOVA juga mengesahkan penambahbaikan yang signifikan dalam HRQoL pada titik masa tersebut. Walau bagaimanapun, di samping perbezaan tersebut, skor min ringkasan masih di bawah penanda aras terendah daripada norma populasi am AS. Kajian ini juga mendapati kesihata mental yang kurang baik dan risiko depresi dalam kalangan penjaga mereka.

Jumlah kos rawatan TB daripada perspektif pembekal dan pesakit adalah MYR 2,218.14. Purata kos pembekal bagi setiap pesakit adalah kira-kira 1.45 kali lebih tinggi daripada bajet yang diperuntukkan oleh Kementerian Kesihatan bagi rawatan kes TB. Walau bagaimanapun, perbelanjaan yang ditanggung oleh pesakit dan penjaga mereka bagi rawatan episod semasa TB tidak membebankan mereka. Purata kos per kontak yang disiasat adalah MYR 21.03. Secara dasarnya, di Malaysia, kes aktif melibatkan hampir 6 kali ganda dari kes TB berasaskan kadar insiden TB setiap tahun.

EVALUATION OF TREATMENT OUTCOME, HEALTH-RELATED QUALITY OF LIFE AND COST OF TREATMENT IN SMEAR POSITIVE PULMONARY TUBERCULOSIS PATIENTS

ABSTRACT

Despite the effective therapy, tuberculosis (TB) remains one of the major causes of adult morbidity and mortality. Available data show that the burden of TB is slowly increasing in Malaysia. Therefore, this study was conducted with an objective to evaluate the management of new smear positive pulmonary TB (PTB) patients. This management included clinical, health-related quality of life (HRQoL) and economic standpoints at the chest clinic of Hospital Pulau Pinang (HPP), Malaysia.

In the first part of this prospective follow-up study, all new smear positive PTB patients who were registered at the chest clinic of HPP, between March 2010 and February 2011, were evaluated for the outcome of their TB treatment. In the second part, new smear positive PTB patients and their family caregivers were invited to self-complete the Short-Form 36 version 2 (SF-36v2) HRQoL questionnaire, while the third part is an incidence-based economic study. The total cost of TB treatment was estimated from the perspective of both provider and patient using appropriate methods.

In this study, there was a 67.26 % TB treatment success rate, whereby 17.56 % patients died during their treatment. With regard to HRQoL scores on the part of new smear positive PTB patients, the study's findings showed that the differences between the SF-36v2 scale scores at the start and end of the treatment were clinically significant (minimal clinically important difference). One-way repeated measures ANOVA analysis also confirmed, at these time points, significant improvement in

HRQoL scores. However, despite these improvements, the mean summary scores were still less than the lowest benchmark of the United States general population norms. Similarly, the study's findings showed the existence of poor mental health and risk of depression among the caregivers of TB patients.

The average cost of TB treatment, from the perspective of both provider and patient, was MYR 2,218.14. The average provider cost was approximately 1.45 times that of the budget allocated by the Ministry of Health for treating a case of TB. The expenses borne by the patients and their families, on the treatment of current episode of TB, were not catastrophic for them. The average cost of contact tracing procedure was MYR 21.03. Active case finding process yielded approximately 6 times more TB cases than the annual incidence rate of TB in Malaysia.

CHAPTER 1

INTRODUCTION

1.1 Tuberculosis

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (M. tb) (World Health Organization, 2013). The bacillus, which is an obligate intracellular pathogen, can infect almost any part of human body. However, lungs are the predominant site of infection. The infection is transmitted from one person to another when an individual with active pulmonary tuberculosis (PTB) sneezes or coughs the bacilli in the form of aerosolized droplets. Because the respiratory droplets remain suspended in the air for many hours, the chances of transmission are higher in crowded and poorly ventilated areas (Beggs, Noakes, Sleigh, Fletcher, and Siddiqi, 2003; Canadian Tuberculosis Committee, 2007; Guo, 2010; Lawn & Zumla, 2011).

When healthy individuals are infected with M. tb, 5–10 % of them are likely to get the disease (World Health Organization, 2002). The remaining 90 % of the infected people live with latent TB infection (LTBI), and never develop disease. The risk of developing active TB is dependent on various factors like number of inhaled bacilli, older age, close contact with an active TB patient, cigarette smoking, alcohol use and the presence of any underlying immune-compromised condition (e.g., the use of immunosuppressant drugs, drug abuse and co-infection with human immunodeficiency virus) (Guo, 2010; Lawn & Zumla, 2011).

The signs and symptoms of TB include those associated with the disease site and non-specific constitutional symptoms like loss of weight (LOW), loss of appetite (LOA), fever, fatigue and night sweats. With regard to PTB, the patients usually present with the history of chest symptoms such as cough (productive or non-productive), chest pain and hemoptysis (Lawn & Zumla, 2011; Ministry of Health, 2012b).

The diagnosis of TB is made through the medical history of the patient, physical examination, imaging and bacteriological results. Usually, it is difficult to diagnose extrapulmonary tuberculosis (EPTB) in that it requires specimen (i.e., tissues or fluids) to be collected from the disease site for cytology/histopathological examination, measurement of adenosine deaminase (ADA) levels, M. tb cultures and real time polymerase chain reaction (PCR). Advanced imaging techniques such as computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) are also used for the diagnosis of EPTB.

The detection of acid-fast bacilli (AFB) on smear and cultures are the most commonly employed diagnostic methods for drug-sensitive PTB. According to the recommendations of World Health Organization (WHO), a suspected PTB patient should submit at least two early morning sputum samples for smear examination in a quality-assured laboratory. Similarly, chest radiography is also the primary modality in the diagnosis of PTB.

Automated liquid culture and sensitivity systems, and nucleic acid amplification tests (NAATs) are the most promising advances in the diagnosis of TB. These tests have become available for not only recovering M. tb from the clinical specimens but also generating drug sensitivity testing (DST) data with a

shorter turnaround time than the agar proportion method (Bemer, Palicova, Rüsch-Gerdes, Drugeon, and Pfyffer, 2002; Lawn & Zumla, 2011; World Health Organization, 2009). Similarly, interferon-gamma release assays (IGRAs) are the most recent advancements in the diagnosis of LTBI. However, tuberculosis skin test (TST), which is a relatively less reliable method, is still used to identify the people whose immune system has been previously exposed to M. tb (Lawn & Zumla, 2011).

Bacille Calmette–Guérin (BCG) is a widely used vaccine against TB. Numerous clinical trials have shown that the protective efficacy of BCG vaccine ranges from 80 % to a negative effect. The variation in the findings of these trials might be a consequence of differences in study design and geographical location. Nevertheless, the vaccine seems to have a protective effect against disseminated forms of TB disease in children (Arbeláez, Nelson, and Muñoz, 2000; World Health Organization, 2013a).

1.1.1 Epidemiology of Tuberculosis

TB is a major public health tragedy. In 2012, an estimated 8.6 million people developed TB (World Health Organization, 2013). With an estimated 1.3 million deaths every year it ranks second major cause of adult mortality from an infectious disease worldwide, after human immunodeficiency virus (HIV) (World Health Organization, 2013). With the emergence of acquired immunodeficiency syndrome (AIDS) epidemic, there was observed an increase in the global burden of TB because these infections are closely linked, and synergize one another. The emergence of multidrug-resistant TB (MDR-TB; M. tb strains resistant to at least isoniazid and rifampicin) and extensively drug-resistant TB (XDR-TB; M. tb strains resistant to isoniazid, rifampicin and any member of quinolone family, and at least one of the

injectable drugs such as kanamycin, capreomycin or amikacin) are further contributions that have fueled the epidemic. It has been estimated that between 2000 and 2020, approximately one billion people will be infected with M. tb, 200 billion infected people will develop active disease and 35 million will die from TB if prevention and control plans are not further developed and executed (Guo, 2010; World Health Organization, 2012).

It is well known that TB is a disease of people with low socioeconomic status, and those with inadequate access to health care facilities. According to a recent report, TB is most common in developing countries (World Health Organization, 2012). In 2011, approximately 60 % of TB cases occurred in Asia, followed by 26 % of cases in Africa. Thereafter, smaller proportions of cases occurred in the Eastern Mediterranean Region (7.70 %), the European Region (4.30 %) and the Region of the Americas (3 %). The 22 high burden countries alone share 82 % of incident cases globally. In 2011, five countries with the largest incidence of cases were India, China, South Africa, Indonesia and Pakistan (in decreasing order). India and China alone share 26 % and 12 % of worldwide TB cases, respectively (World Health Organization, 2012).

Malaysia is situated in the Western Pacific region of WHO, and is ranked as an intermediate burden TB country (World Health Organization, 2012). In Malaysia, for the last 3 years, the incidence rate of TB has been 80–82 cases per 100,000 population (World Health Organization, 2013). However, the absolute number of new cases has increased from 15,057 in 2000, up to 21,851 in 2012 (World Health Organization, 2013). In 2009, there were 1,582 TB-related deaths, up from 942 in 2000 (United Nations, 2011). Similarly, from 1990 to 2011, the number of cases

with TB-HIV co-infection increased from six to 1,630 (Ministry of Health, 2012a). All of these facts and figures illustrate slowly increasing burden of TB in Malaysia.

1.1.2 Treatment of Tuberculosis

The fundamental objectives of TB treatment are (World Health Organization, 2012):

- To successfully treat the disease.
- To restore quality of life and productivity.
- To stop the transmission of M. tb.
- To prevent the chances of relapse.
- To prevent the development and transmission of MDR-TB.

However, from the patient and provider perspectives, this task is somewhat challenging because it requires a complex treatment regimen for at least 6 months (Bass *et al.*, 1994). To counter these treatment challenges, WHO introduced, in mid-1990s, a directly observed therapy (DOT). The five core components of DOT include:

i. Political commitment with adequate financing.
ii. Early diagnosis through quality assured sputum smear microscopy.
iii. An uninterrupted supply of first-line anti-TB drugs.
iv. Provision of the standardized treatment regimen under supervision.
v. Evaluation of the case detection and outcome of treatment.

Within a decade, almost all countries adopted the DOT strategy, and there was a substantial progress towards global targets set for 2005 (i.e., detection of at least 70

% of estimated smear positive PTB cases and a successful outcome of 85 % of these cases). For the first time, the global target of 85 % treatment success rate was achieved in 2005 (World Health Organization, 2012).

In 2006, WHO launched the Stop TB Strategy to strengthen TB care and control. This strategy was linked to the new global targets which were set for 2015 as a part of the Millennium Development Goals (MDGs). According to these targets, there should have a decreasing trend in the incidence of TB by 2015, and in comparison to the levels in 1990 there needs to be a 50 % reduction in the prevalence and mortality rates associated with TB. These targets were endorsed and described in the Global Plan developed by the Stop TB Partnership. The latest Global Plan to Stop TB covers the period from 2011 to 2015, and states that the treatment success rate (in annual cohort) should not be less than 90 % (World Health Organization, 2012).

In 1961, Malaysian government launched its National Tuberculosis Program (NTP) (Iyawoo, 2004). The country and state TB control programs are headed by the Director General of Health and the state Director of Health, respectively. The organizational structures for the national and state TB control programs are given in Figure 1.1 and Figure 1.2, respectively.

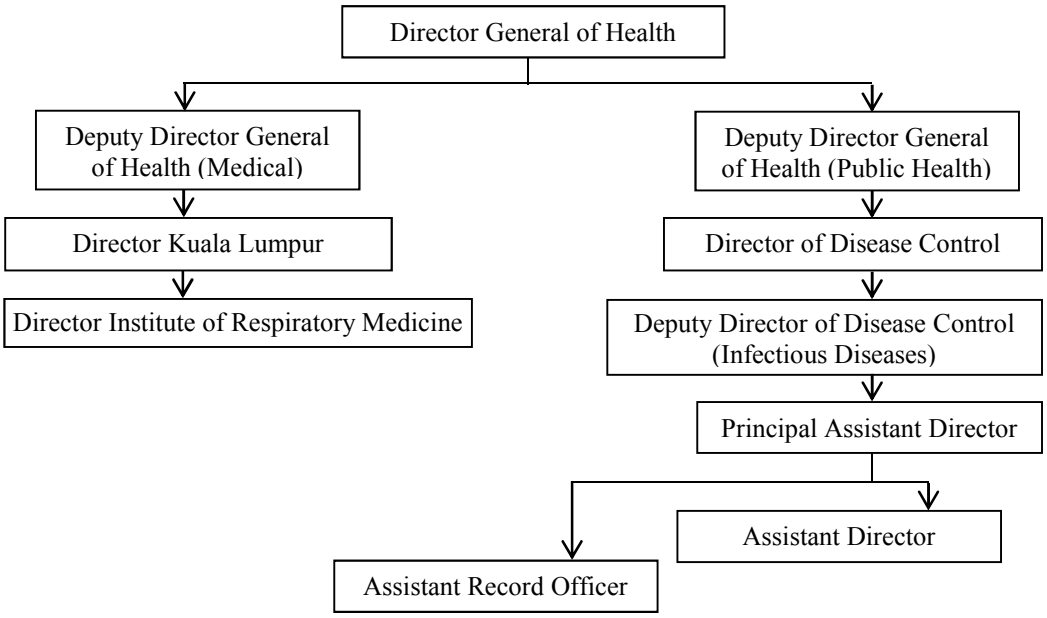

Figure 1.1. Organization chart of the tuberculosis program in Malaysia. Adapted from "tuberculosis in Malaysia: problems and prospect of treatment and control" by Kuppusamy Iyawoo, 2004, *Tuberculosis, 84*, 4-7. Copyright [2004] by Elsevier. Reproduced with permissions (License number: 3150600709370).

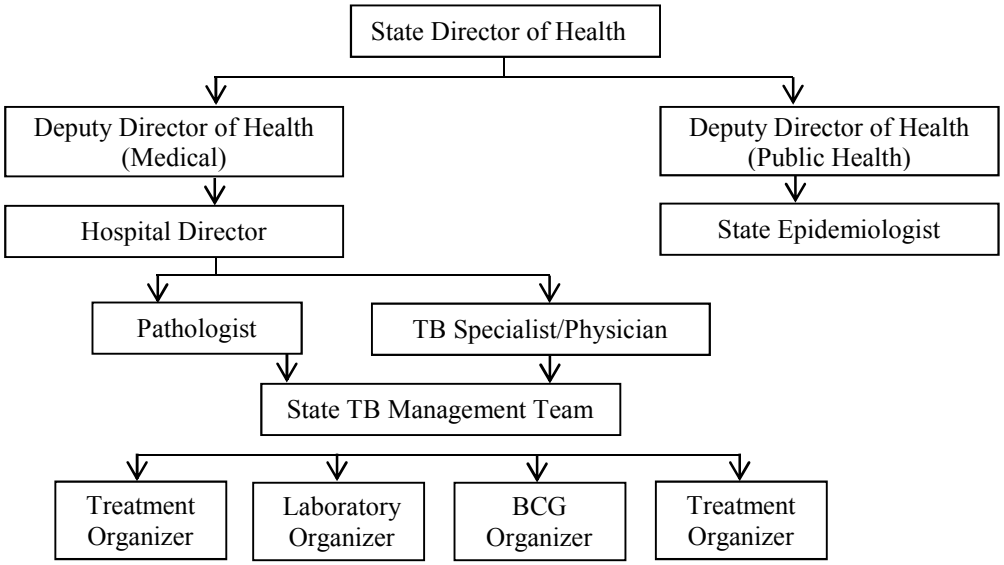

Figure 1.2. Organization chart of the tuberculosis program in each state of Malaysia. Adapted from "tuberculosis in Malaysia: problems and prospect of treatment and control" by Kuppusamy Iyawoo, 2004, *Tuberculosis, 84*, 4-7. Copyright [2004] by Elsevier. Reproduced with permissions (License number: 3150600709370).

1.1.2.1 Standard Anti-Tuberculosis Drugs

Table 1.1 provides details of essential first-line anti-TB drugs including their recommended doses and common side effects. As this study includes only new smear positive PTB patients, the detail of treatment regimen is based on this sub-group of patients.

Table 1.1
Recommended Doses of First-Line Anti-Tuberculosis Drugs in Adults, and their Side Effects

Drug	Recommended dose				Common side effects
	Daily		Three times per week		
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Maximum (mg)	
Isoniazid*	5 (4–6)	300	10 (8–12)	900	Skin rashes, jaundice, hepatitis, anorexia, nausea, abdominal pain, burning sensation and numbness or tingling sensation in the hands or feet
Rifampicin	10 (8–12)	600	10 (8–12)	600	Skin rashes, shock, purpura, jaundice, hepatitis, anorexia, nausea, abdominal pain, orange or red urine, acute renal failure and flu syndrome
Pyrazinamide	25 (20–30)	2000	35 (30–40)	3000	Skin rashes, jaundice, hepatitis, anorexia, nausea, abdominal and joint pain
Ethambutol	15 (15–20)	1600	30 (25–35)	2400	Visual impairment
Streptomycin	15 (12–18)	1000	15 (12–18)	1500	Skin rashes, deafness, dizziness and decreased urine output
	10 for > 60 years old	750 for > 60 years old	10 for > 60 years old	1000 for > 60 years old	

*Pyridoxine should be added when isoniazid is prescribed. *Notes.* Modified from Management of Tuberculosis: Clinical Practice Guidelines (3rd ed.), Ministry of Health Malaysia, 2012, Putrajaya, Malaysia: Malaysia Health Technology Assessment Section (MaHTAS). Copyright [2012] Malaysia Health Technology Assessment Section. Reproduced with permission.

Fluoroquinolones (i.e., ofloxacin, levofloxacin, moxifloxacin) are the most common second-line anti-TB drugs used in non-hepatotoxic anti-TB regimens. Table 1.2 provides details of recommended doses of fluoroquinolones, and their common side effects.

Table 1.2
Recommended Doses of Fluoroquinolones in Adults, and their Side Effects

Drug	Daily dose (mg/kg body weight	Maximum dose (mg)	Frequency	Common side effects
Ofloxacin	15–20	1000	Twice daily (common dose is 400 mg two times in a day)	Gastrointestinal intolerance, headache, malaise, insomnia, restlessness, dizziness, allergic reactions, diarrhea and photosensitivity
Levofloxacin	7.5–10	1000	Daily (common dose is 750 mg in a day)	
Moxifloxacin	7.5–10	400	Daily (400 mg)	

Notes. Modified from Management of Tuberculosis: Clinical Practice Guidelines (3rd ed.), Ministry of Health Malaysia, 2012, Putrajaya, Malaysia: Malaysia Health Technology Assessment Section (MaHTAS). Copyright [2012] Malaysia Health Technology Assessment Section. Reproduced with permission.

Isoniazid, pyrazinamide and rifampicin are the most common anti-TB drugs known to cause hepatic damage. The management of liver damage caused by anti-TB drugs depends on the severity of damage, severity of TB, capacity of health care unit to treat side effects and the phase of TB treatment.

If it is confirmed that hepatitis is caused by first-line anti-TB drugs, the treatment should be immediately stopped. Clinicians should wait until liver function tests are normalized and clinical symptoms (e.g., nausea and abdominal pain) are resolved. Then, first-line anti-TB drugs should be reintroduced one at a time. It is recommended to start with rifampicin because it is less likely to cause hepatotoxicity than isoniazid and pyrazinamide, and is the most effective agent (Centers for Disease Control and Prevention, 2003; Saukkonen *et al.*, 2006). Isoniazid should be

introduced (within a week) after the rifampicin. If the patient is able to tolerate both rifampicin and isoniazid, the introduction of pyrazinamide should be avoided.

1.1.2.2 Standardized Treatment Regimens

The treatment of TB is divided into two phases: the intensive phase (IP) and continuation phase (CP). In relation to the standard treatment, WHO strongly recommends 2HRZE/4HR regimen (isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) for 2 months during the IP / isoniazid (H), rifampicin (R) for 4 months during the CP) in newly diagnosed smear positive PTB patients. However, provided that the patient is neither HIV positive nor living in HIV prevalent settings, an alternate therapy is 3 times weekly dosing throughout the therapy [$2(HRZE)_3/4(HR)_3$] (3 times weekly isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) for 2 months during the IP / 3 times weekly isoniazid (H), rifampicin (R) for 4 months during the CP). Similarly, during the CP of the treatment, patients with isoniazid-resistant TB may be prescribed 4HRE therapy (Ministry of Health, 2012b; World Health Organization, 2009).

With regard to co-management of HIV and active TB disease, WHO now recommends the use of 2HRZE/4HR therapy. Three times weekly dose during the IP is no longer recommended owing to 2–3 times higher chances of relapse and treatment failure in HIV co-infected patients. However, an acceptable alternative is 3 times weekly therapy during the CP. Nevertheless, co-trimoxazole should be started in HIV positive TB patients as a preventive measure against Pneumocystis jirovecii, the malarial parasite and a range of bacterial infections (World Health Organization, 2009).

Compliance to the standard anti-TB regimen is critical for the success of treatment. To enhance the compliance among TB patients, WHO has recommended using fixed-dose combinations (FDCs) of anti-TB drugs. Studies have shown that compared with separate-drug regimens, FDCs reduce the risk of non-compliance by 17 % (Bangalore, Kamalakkannan, Parkar, and Messerli, 2007). In addition, FDCs are thought to reduce the acquisition of drug resistance because patients cannot be selective in their choice of drugs to ingest. Similarly, prescription errors are less likely to happen with FDCs because the dosage recommendations are uncomplicated and adjustment in the dosage, according to patient body weight, is easier (World Health Organization, 2009).

The two FDCs, available in Ministry of Health (MOH) Malaysia Drug Formulary, are (Ministry of Health, 2012b):

i. Four-drug combination tablet: isoniazid 75mg, rifampicin 150mg, ethambutol 275mg and pyrazinamide 400 mg.
ii. Three-drug combination tablet: isoniazid 75mg, rifampicin 150mg and pyrazinamide 400 mg.

These FDCs are prescribed during the IP of the treatment. The recommended doses for the available combinations are as follows:

- 30–37 kg body weight: 2 tablets daily.
- 38–54 kg body weight: 3 tablets daily.
- 55–70 kg body weight: 4 tablets daily.
- More than 70 kg body weight: 5 tablets daily.

1.1.2.3 Monitoring Drug Treatment

Response to TB treatment in a new smear positive PTB patient is usually monitored by sputum smear examination at the end of the IP of the treatment. Additional sputum smear microscopy is required at the third month if sputum smear was positive at the end of second month of the treatment. However, despite the sputum positivity at the end of second month, it is recommended not to extend the IP of the treatment. Smear positivity at the end of fifth or sixth month of the treatment is considered as treatment failure. In such a case, patients should be further tested using sputum culture and DST, and their treatment should be restarted.

It is notable that the fourth edition of TB treatment guidelines recommends a limited use of culture and DST for the new patients presumed to have drug-susceptive TB. However, if the patient belongs to a setting with high prevalence of isoniazid resistance, or if the patient has established active TB after known contact with a patient having drug-resistant TB, culture and DST should be performed at the start of the treatment. Another important recommendation of WHO is mandatory screening of all TB patients for HIV co-infection (World Health Organization, 2009).

1.1.2.4 Supervision and Patient Support

The Patients' Charter for TB Care states that patients are the active recipients of health care services. They have the right to seek information, care, privacy, dignity, food supplements and other type of incentives. On the other hand, patients have the responsibility to share their complete information with the health care

providers, following the treatment, sharing in community health and exchanging the experiences gained during the treatment with others in a community.

Ideally, anti-TB drugs should be administered under the direct supervision of DOT staff to ensure that the patient takes right anti-TB drugs in right doses at right intervals. However, to ensure completion of the treatment, the strategy to manage a TB patient should be context-specific and patient-friendly. For example, if for certain reasons, (e.g., psychologically handicap patients, prisoners, those unable to come DOT center due to transportation problems, etc.) the patients are unable to receive a daily therapy at the DOT clinic, efforts should be made to overcome the barriers through community involvement. In this context, supporter of the treatment may be the cured TB patients, close relatives, colleagues, religious leaders, general medical practitioners, neighbors, community pharmacists and traditional healers. However, the NTP staff is responsible for training and monitoring the non-medical treatment supporters (World Health Organization, 2009).

1.2 Analysis of Treatment Outcome

WHO has set various benchmarks to evaluate the performance of NTP in order to take appropriate and timely actions to control the burden of the disease. Among these, WHO uses analysis of TB treatment outcome as an important yardstick.

In most parts of the world, standard categories are used to report the outcome of TB treatment (World Health Organization, 2009). However, based on some logical grounds, some European countries have modified the WHO outcome criteria (Antoine, French, Jones, and Watson, 2007; Ditah *et al.*, 2008). Nevertheless, whatever outcome criteria is used, it allows the NTP mangers to identify specific

problem which if addressed properly could improve the success rate of TB treatment. For example, a higher proportion of the patients in default outcome category indicate that the health care managers must adopt appropriate strategies to ensure the patients' adherence to TB treatment.

1.3 Health-Related Quality of Life Assessment

WHO defines 'health' as a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity (World Health Organization, 2003b). Although there are many types of equipment and instruments to measure clinical and bio-physiological parameters of health, researchers and clinicians have now realized that these only measure intermediate outcomes which might not reflect the patients' understanding of their own well-being. Nowadays, it is known that an individual's perception of his/her physical, mental and social well-being could be measured in terms of health-related quality of life (HRQoL) (Spilker, 1996).

According to a recent systematic review and meta-analysis, numerous studies have reported altered physical and mental health on the part of TB patients (Bauer, Leavens, and Schwartzman, 2012). These studies have used a variety of instruments to gauge the HRQoL of TB patients. In general, a valid and reliable HRQoL measurement instrument is important to guarantee the accuracy, precision and generalizability of the results. Whilst more research is required to develop a valid disease-specific tool for TB patients, monitoring even their HRQoL through a generic questionnaire like the Short-Form 36 version 2 (SF-36v2) could help health care professionals to target the specific mental and physical health components which are adversely affected by the disease or treatment. Likewise, this measurement

could be used to predict how certain physiological, psychosocial, sociological, economic and spiritual factors influence a patient's well-being (Rajeswari, Muniyandi, Balasubramanian, and Narayanan, 2005). Moreover, it would also allow health care professionals to identify the patients who, due to disease, are at a higher risk of altered HRQoL. Stratifying such patients is of critical importance in countries where, either due to limited resources or higher TB incidence, a highly individualized approach cannot be applied.

1.4 Cost of Tuberculosis Treatment

The intricacy and cost of TB treatment have risen in the recent years. The emergence of MDR-TB, longer duration of TB treatment in HIV seropositive patients, higher treatment failure rates in difficult-to-reach patients (i.e., drug abusers, immigrants, etc.) and increasing demands of DOT programs contribute to higher costs of TB treatment (Eliud, Bjarne, and Odd, 2005; Wurtz & White, 1999). This has, therefore, put an extra pressure on health care budgets. According to one estimate, approximately 70–80 % of TB cases are within the most productive age group (15–54 years of age), and thereby the resultant economic loss to a society is very high (Othman, Ibrahim, and Raja'a, 2012; World Health Organization, 2012).

Numerous studies have reported that patients and their families have to bear direct and indirect costs of TB (Aspler *et al.*, 2008; Rajeswari, Balasubramanian, Muniyandi, Geetharamani, Thresa, and Venkatesan, 1999; Sinanovic, Floyd, Dudley, Azevedo, Grant, and Maher, 2003). In many countries, TB patients seek initial assistance from traditional healers or private health care sector either because of lack of disease-related knowledge or preference of private health care sector due to the perception that, compared with public providers, private providers are convenient,

concerned and competent. Loss of earning due to illness and/or earlier mortality due to TB are usually greater than direct cost of TB treatment (World Health Organization, 2000).

On top of the economic costs, TB causes social and psychological costs. TB patients may be rejected by the friends and family, or may be abstained from their jobs. Such discrimination may result in depression, anxiety and diminished HRQoL (World Health Organization, 2000).

The Global Plan to Stop TB 2011-2015 sets out the funding needed for the implementation of TB care and control in low- and middle-income countries. According to a recent report by WHO, an estimated amount of United States Dollars (USD) 8 billion (in 2012 dollars) will be required, in 2015, for the diagnosis and treatment of various forms of TB (World Health Organization, 2012). Malaysia has already adopted the WHO Stop TB Strategy, and is working on a National Strategic Plan for TB control 2011 to 2015. Consequently, Malaysian government has allocated a total of USD 15 million (in 2012 dollars) for the free provision of TB care through the network of public health care facilities. In Malaysia, the budget of NTP is funded from the domestic sources without any contribution from the Global Fund (United Nations, 2011; World Health Organization, 2012).

1.5 Problem Statement

The current NTP of Malaysia is functioning in line with the recent guidelines of WHO, though have not been fully integrated in many parts of Peninsular Malaysia (United Nations, 2011). In 2007, Malaysia surpassed the 70 % target in terms of detection of new smear positive cases. However, over the past years, there was

observed a decreasing pattern in TB treatment success rates (Nik, Mohd, Wan, Sharina, and Nik, 2011; United Nations, 2011). A recent global TB report documented that, over the last decade, TB cure rate was below 80 % in Malaysia (World Health Organization, 2012). The failure to achieve the given target was partially due to a higher proportion of patients lost follow-up and the weakness in data management (United Nations, 2011). Another reason might be the pressure exerted on the health care system due to an increasing number of cases over the past years (United Nations, 2011; World Health Organization, 2012). With all of these findings, it appears that there is still a room for improvement especially in terms of making efforts to decrease the absolute number of annual TB cases, and to achieve a better treatment success rate (Iyawoo, 2004).

At present, much of the attention within TB management is spent on microbiological cure, and its impact on HRQoL is either undervalued or seldom considered (Marra, Marra, Cox, Palepu, and Fitzgerald, 2004). Even, the most recent guidelines on the management of TB are silent on this critical aspect (World Health Organization, 2009). Existing literature shows that TB has substantial and encompassing impact on the HRQoL of the infected patients. Stigma associated with TB is a known factor which might affect patients' mental well-being and life roles in a community. Likewise, many patients have reported anxiety and depression even after the completion of their TB treatment (Chamla, 2004; Guo, Marra, Marra, Moadebi, Elwood, and FitzGerald, 2008).

The Patients' Charter for TB Care allows the patients to evaluate the program's performance (World Health Organization, 2006b). From the patients' perspective, one of the major performance indicators might be the NTP's capability to address the

physical and mental well-being of the patients. Therefore, the assessment of HRQoL of TB patients, as an additional indicator of performance, will add value to the NTP.

Besides the worth of knowing prevalence and incidence rates for weighing the burden of TB and highlighting the gravity of the epidemic, these pointers may fail to explain the trends in the societal and economic burden of the disease (Ogden, 2000). Therefore, it is crucial not only to highlight the importance of increasing TB incidence rates, but also to address the structural and economic barriers which may be acting together to fuel the epidemics (Aspler *et al.*, 2008; Floyd, Blanc, Raviglione, and Lee, 2002; McIntyre, Thiede, Dahlgren, and Whitehead, 2006).

The economic impact of TB is often measured in terms of direct and indirect costs to the public health care services. These include the costs of medication, employees and other health care facilities (World Health Organization, 2000). Assessing the utilization of health care resources at governmental level is always important in terms of provision of long-term planning in a highly dynamic health economy (Wurtz & White, 1999). Furthermore, cost estimates are increasingly required by insurance companies, government payers and others groups which are alert to the allotment of limited research and treatment dollars.

In order to fully understand the impacts of TB on the well-being of the members of society, there is a need to take into account the costs tolerated by the patients, their families and communities. Nevertheless, these are occasionally overlooked in favor of reducing the expenses of governmental agencies such as departments of health (World Health Organization, 2000). In these circumstances, too little investment occurs, and it may be allocated in a way which does not minimize the burden of the disease. Moreover, this strategy does not enable the

clinicians and NTP managers to make efficient health care choices (World Health Organization, 2000).

1.6 Rationale of the Study

To justify the design and conduct of this study, the logical basis of each study objective is given separately.

1.6.1 Analysis of Treatment Outcome

Assessment of treatment outcome of newly diagnosed smear positive PTB patients is used as a major pointer to gauge the effectiveness of NTP. It enables the NTP managers and staff to identify the problems, and take adequate and timely actions to improve the overall performance of the program (Diel & Niemann, 2003; Helbling, Medinger, Altpeter, Raeber, Beeli, and Zellweger, 2002; World Health Organization, 2009).

WHO has recommended that countrywide cohort analysis of TB treatment outcome should be performed every year. Furthermore, it is strongly recommended that new smear positive PTB patients and previously treated patients (i.e., relapses, defaulters and treatment failures) should be analyzed as separate cohorts because of their different characteristics and probable results. WHO further recommends that the treatment outcome should be monitored at peripheral, district, state and national levels. Indeed, this strategy could identify the states or units which are performing well, and thus would enable the NTP staff to replicate the successful practices elsewhere (World Health Organization, 2009).

According to a recent report by WHO, TB treatment success rate for new smear positive PTB patients in Malaysia is still below the global success target of 85 % (World Health Organization, 2012). This report also highlights that the outcome category death is one of the major reasons for non-attainment of the given target for the treatment success. To date, a few studies from different states of Malaysia have reported the treatment outcome of TB patients with a very high heterogeneity in the results (Abdullah, Sulaiman, Ahmed, Muttalif, and Qais, 2011; Ismail & Bulgiba, 2013; Nik *et al.*, 2011). Moreover, none of these studies have separately reported the treatment outcome of new smear positive PTB patients. Indeed, this is the priority group in terms of evaluating the performance of NTP.

Furthermore, most of the studies were conducted at the time when the patients were notified and managed based on preceding TB treatment guidelines (World Health Organization, 2003a). In addition, none of these studies have explored a relationship between patient characteristics and mortality during TB treatment. Similarly, the existing data are also lacking in terms of establishing a relationship between patient characteristics and duration of TB treatment.

Based on the recommendations of WHO and the gaps in existing literature, one could understand why it is urgent to conduct cohort analysis of new smear positive PTB patients in the local settings.

1.6.2 Health-Related Quality of Life Assessment

With the advent of effective treatment strategies, the emphasis of TB management has shifted from prevention of mortality to evasion of morbidity. To attain this target, a client-oriented comprehensive NTP should address the social and

emotional impact of the disease, and should adopt support strategies to enhance the acceptance (Marra *et al.*, 2004; Rajeswari *et al.*, 2005).

The existing literature shows that, amongst TB patients in the Malaysian population, there is a paucity of research with regard to their HRQoL. Likewise, only two follow-up studies from Asia have reported changes in HRQoL with TB treatment, although none used a widely acceptable HRQoL assessment tool (Dhingra & Rajpal, 2005; Rajeswari *et al.*, 2005). Moreover, there is nothing in the existing literature regarding the assessment of HRQoL in the family caregivers of TB patients.

One of the benefits of SF-36v2 norm-based scoring (NBS) is that it allows general and simplified interpretation of the observations. In NBS, each scale is scored using the same mean (50) and the same standard deviation (10 points) as found in the United States (U.S.) general population. However, questions arise on equivalence of the SF-36v2 standard (U.S. weights) scoring algorithms in the Malaysian population. Therefore, it was deemed necessary to conduct a study aiming to find out whether or not the Malaysia-specific scoring algorithms would give results (scores) equivalent to those of the standard scoring algorithms. Equivalence in results implies that instead of the country-specific approach, the U.S. standard SF-36 summary scales (i.e., physical component summary and mental component summary) and scoring algorithms could be used in the Malaysian population (Lam, Tse, Gandek, and Fong, 2005; Ware *et al.*, 1998).

1.6.3 Cost Analysis

The basic underlying condition for an efficient allocation of the resources is to know the financial cost of the disease. Without analyzing the costs, it is impossible to contemplate or improve the efficiency of disease-control projects. In particular, the ongoing reforms and decentralization processes in the health care systems of developing countries require precise cost information (Su, Sanon, and Flessa, 2007). For the most part, health care organizations use cost accounting for the estimation of unit cost of their services, which helps them to plan a realistic budget and price for the service (Sumeet, Kanchan, and Sonal, 2010).

Studies from developing countries have demonstrated that an average cost for the treatment of a drug susceptible TB case ranged from USD 94.00 to USD 2058.00 (Aspler *et al.*, 2008; Ayé, Wyss, Abdualimova, and Saidaliev, 2010; Elamin, Ibrahim, Sulaiman, and Muttalif, 2008; Eliud *et al.*, 2005; Okello, Floyd, Adatu, Odeke, and Gargioni, 2003; Othman *et al.*, 2012; Rajeswari *et al.*, 1999; Sinanovic *et al.*, 2003). Similarly, studies from developed countries have shown a considerable fluctuation in the average cost of TB treatment (Rubado, Choi, Becker, Winthrop, and Schafer, 2008; Wurtz & White, 1999). The above mentioned data referring to the cost of TB treatment is highly divergent because of differing health care systems, perspectives (i.e., provider and patient), costs components, and methods of calculation and data collection. This means that these pieces of data are neither transferable nor any of implications arising from these studies can be applied to the local settings (Diel, Rappenhöner, and Schaberg, 2004).

Wurtz & White (1999) have stressed the need to assess the resource utilization pattern in TB due to following important reasons:

- To evaluate the relative contribution of outpatient and inpatient treatment to the cost of TB diagnosis and treatment.
- To evaluate the relative contribution of different phases of treatment to the cost of TB care.
- To provide long-term planning in changing health economy.

Notably, health system costs associated with tracing contacts of smear positive PTB patients (index cases) are often neglected in most of the economic studies. Indeed, data on costs and practicality of contact tracing can provide useful information to the policymakers for taking appropriate measures to control the slowly growing incidence rate and burden of the disease (Aspler *et al.*, 2008; United Nations, 2011). However, to date, no study from Malaysia has reported the cost and practicality of contact tracing.

According to the economic findings, methodological concerns in comparing various cost studies and scarcity of cost data on the management of newly diagnosed smear positive PTB patients, one can understand why it is urgent to conduct this type of economic evaluation in Malaysia. Currently, there is a gap in the Malaysian literature concerning a comprehensive economic analysis of TB patients.

1.7 Research Contribution

A gradual increment in absolute number of TB cases in Malaysia is increasing pressure on the NTP. Without any doubt, the achievement of 85 % treatment success rate, provision of appropriate services to TB patients and maintaining the average cost of TB treatment within allocated budget are the key challenges for the clinicians and NTP managers.

Within this context, it can be assumed that a study focusing on the above mentioned issues is critical and timely. This study is expected to make following unique research contributions that might be helpful for the policymakers in the local and/or international settings:

- The study will describe socio-demographic, clinical and treatment characteristics of smear positive PTB patients, and their treatment outcome over a 1-year period. Moreover, this study will also underline the risk factors for poor treatment outcome.
- This study will also describe the practices of the clinicians in relation to the recent guidelines on the treatment of TB. Moreover, this study will provide the policymakers with the empirical data required to decide whether the standard treatment outcome criteria should be used or it needs to be modified, as some of the European countries did, for a more objective evaluation of the performance of NTP.
- This study will provide the evidence that whether the SF-36v2 standard (U.S. weights) scoring algorithms and the U.S. standard summary scales can be used in the Malaysian population.
- The findings of the study will highlight the impact of TB treatment on the HRQoL of patients. Evidences of poor HRQoL among TB patients will suggest that current practices of Malaysia's NTP are unable to address the psychological and social well-being of the patients. Indeed, this baseline data will enable the NTP managers to decide the assessment of HRQoL in TB patients, as an added parameter, to evaluate and improve the NTP's performance.